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By J Lukerchuetz

AMENDMENT UNDER 37 CFR 1.116
EXPEDITED PROCEDURE -
EXAMINING GROUP 1812

PATENT

Attorney Docket No. 11823-18

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

NICHOLAS F. LANDOLFI

Serial No.: 07/532,267

Filed: June 1, 1990

For: CHIMERIC LIGAND/ IMMUNOGLOBULIN MOLECULES AND THEIR USES

Examiner: G. Draper

AMENDMENT AFTER FINAL

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Sir:

In response to the Final Office Action mailed February 10, 1993 (Paper No. 13), please amend this application as follows:

IN THE CLAIMS:

Please cancel claims 1, 11, 12, 13 and 14 without prejudice to subsequent renewal.

Please amend the following claims as indicated:

2. (Amended) An immunoligand of claim [1] ~~25~~ wherein the constant region component is a heavy chain constant region.

5. (~~Twice Amended~~) An immunoligand of claim [1] ~~25~~, wherein the ligand component is linked to the constant region component via a peptide bond to a hinge region of said constant region component.

6. (~~Amended~~) An immunoligand of claim [1] ~~25~~ wherein the immunoligand is capable of fixing complement through the constant region component.

7. (~~Amended~~) An immunoligand of claim [1] ~~25~~ 1 wherein the immunoligand is capable of mediating antibody dependent cell cytotoxicity through the constant region component.

8. (~~Amended~~) An immunoligand of claim [1] ~~25~~ 1 wherein the ligand component is a naturally occurring interleukin-2.

~~25~~ 11. (Amended) An immunoligand [comprising interleukin-2 linked to a human IgG1 heavy chain constant region] of claim 3, wherein [the interleukin-2] the sequence comprises an additional C-terminal hydrophilic residue [and is capable of binding an interleukin-2 receptor].

~~12~~ 13. (Twice Amended) A pharmaceutical composition comprising a suitable carrier and an immunoligand of [claims 1 or 12] claim ~~25~~ 1, wherein the immunoligand binds to an interleukin-2 receptor.

PLEASE ADD THE FOLLOWING NEW CLAIM:

~~25~~. 1 ~~An~~ A chimeric immunoligand comprising:

an interleukin-2 ligand component comprising an interleukin-2 amino acid sequence capable of binding an interleukin-2 receptor; and

an immunoglobulin constant region component comprising an immunoglobulin constant region domain without an immunoglobulin variable region domain;

wherein the ligand component and the constant region component are in peptide linkage, the immunoligand is capable of binding to an interleukin-2 cell surface receptor through the ligand component, and the immunoligand is capable of fixing complement and/or mediating antibody dependent cell cytotoxicity through the constant region component, due to binding of the immunoligand to the cell surface receptor.

REMARKS

Claims 2-10, 15, 23 and 25 are pending. Note that new claim 25 is based on cancelled claim 1 but differs in three respects. First, additional language has been added to clarify that the constant region component is lacking a variable domain. Support for this amendment ~~is~~ provided by the specification at

page 6, lines 7-9 and lines 31-34. The specification explains that the ligand component replaces all or substantially all of the immunoglobulin variable domain, and that the constant region component therefore usually contains ten or fewer amino acids from the variable region. Second, an additional limitation has been added specifying that the immunoligand is capable of mediating complement fixation or ADCC through the constant region component due to binding of the immunoligand to the cell surface receptor. Support for this amendment is provided throughout the specification, for example p. 8, lines 31-32 and pp. 23-24. Third, the format of claim 25 has been somewhat modified from that of claim 1 for ease of comprehension.

The Examiner has rejected claim 8 under 35 USC §112, fourth paragraph for failing to further limit the subject matter of a previous claim. In response, Applicant has amended claim 8 to clarify that it specifies an additional limitation over claim 1, namely that the ligand component is a naturally occurring IL-2 ligand. Support is provided at page 7, line 10 of the specification.

The only other outstanding rejection against the pending claims is that the Examiner has stated that they are obvious under 35 USC §103 over Von Wussow. All other rejections have become moot in view of the claim cancellations.

The Invention

The invention, as specified in claim 25, is directed to an immunoligand comprising an IL-2 ligand and a constant region of an immunoglobulin chain. The IL-2 ligand is peptide bonded to the constant region. The immunoligand is capable of binding to the IL-2 receptor through the IL-2 component and of fixing complement and/or mediating ADCC through the constant region component due to binding of the IL-2 component.

Von Wussow

Von Wussow discusses production of an INF-α complex by chemical crosslinking of purified INF-α ligand and an intact immunoglobulin to form a product that is not in peptide linkage.

Von Wussow also mentions that other ligands potentially be used in place of IFN-α, but does not exemplify these alternative chemically crosslinked complexes. Von Wussow reports that the INF-α/immunoglobulin complex has a longer serum half-life than free INF-α. Von Wussow does not describe any tests to establish whether his complex could mediate complement-dependent lysis or ADCC due to binding of the INF-α moiety to its receptor, nor does he recognize the utility of these properties in any fusion proteins.

Von Wussow distinguished

The Examiner states that von Wussow specifically teaches IL-2 and INF as functional equivalents in this context. The Examiner states that contrary to Applicant's prior arguments, it is well known in the art that IFN mediates ADCC and complement-mediated lysis. The Examiner also notes that the biological activity of the various immunoligands is not the controlling issue of obviousness. Applicant respectfully traverses this rejection.

Von Wussow does not disclose at least two important structural features of the claimed IL-2 immunoligands. In the claimed immunoligands, the ligand portion is attached to the constant region of an immunoglobulin chain (thereby replacing substantially all of the immunoglobulin's natural variable region) by a peptide bond. By contrast, in Von Wussow's complex, the ligand portion is attached to an intact immunoglobulin, at a presumably random location, by chemical cross-linking. Applicant agrees with the Examiner that Von Wussow mentions, albeit prophetically, that an immunoglobulin complex might also be constructed from an IL-2 ligand in place of the INF-α ligand exemplified. However, patentability over Von Wussow is not premised merely on the difference between IL-2 and INF-α, but rather on the difference between an immunoglobulin chain constant region and an intact immunoglobulin, and the difference between a peptide linkage and a chemical cross-linkage. These structural differences from the claimed immunoligands exist irrespective of the particular ligand used in Von Wussow's complex.

The claimed immunoligands exhibit several advantages that the complexes discussed by Von Wussow have not been shown to possess. These advantages are relevant to patentability in that acquisition of advantageous functional properties substantiates the nonobviousness of underlying structural modifications. A major advantage of the claimed immunoligands is that they confer the IL-2 cell surface receptor binding-specificity of the IL-2 ligand moiety, and the effector functions of the immunoglobulin constant region moiety responsive to binding of the IL-2 ligand moiety to its receptor. Thus, the claimed immunoligands are functionally very similar to natural immunoglobulins, but with the added advantage that binding specificity and affinity is predetermined by choice of the IL-2 ligand. By contrast, Von Wussow's complex, which retains the immunoglobulin moiety variable region, will bind either to an antigen recognized by the ligand moiety and to an unrelated antigen recognized by the immunoglobulin moiety. Moreover, Von Wussow provides no indication that the immunoglobulin moiety of his complex has capacity to mediate effector functions responsive to binding of the ligand moiety. Nor would such capacity appear particularly likely to exist in view of the unnatural chemical cross-linkage between the ligand and immunoglobulin moieties. Presumably, this unnatural linkage lacks the capacity to transduce conformational changes that occur on ligand binding, and which may be important for effector function such as ADCC and complement fixation.

The Examiner's observation that it is well known that INF stimulates ADCC does not imply that Von Wussow's INF-α-complex exhibits effector functions analogously to the claimed IL-2 immunoligands. IFN-α effects a generalized (i.e. nonantigen-specific stimulation) of ADCC via macrophage activation. See Paul, Fundamental Immunology (2d ed. 1989) at p.649. Thus, it is likely that the INF-α moiety of Von Wussow's complex acts in the same manner as free INF-α to effect a generalized stimulation of ADCC activity on binding of the immunoligand to macrophages. However, this stimulation would be a result of the IFN-α ligand possessing INF-α activity, not as a result of its conjugation to an immunoglobulin. This INF-α-

mediated generalized stimulation is entirely different from complement-dependent cytolytic activity or ADCC effected by the claimed IL-2 immunoligands. Here, binding of the IL-2-immunoligand to its receptor induces binding of complement and/or cytolytic cells specifically to the IL-2-immunoligand and not a generalized stimulation of cytolytic activity toward any bound antibody. Accordingly, the claimed IL-2 immunoligands can be used to eliminate a specific class of cells bearing their receptor, an advantage not conferred by generalized INF-α stimulation of ADCC activity. Moreover, if the INF-α of Von Wussow's complex were substituted with an IL-2 ligand, the new complex would not of course even be capable of inducing generalized stimulation of ADCC via the INF-α ligand.

Further advantages conferred by the claimed immunoligands over Von Wussow's complex are ease of production and reproducibility of therapeutic application. The claimed immunoligands can be produced as homogenous polypeptides of predetermined structure from a single recombinant DNA expression system. By contrast, preparation of Von Wussow's complex requires separate purification of ligand and immunoglobulin, a chemical cross-linking reaction, and purification of cross-linked product. Moreover, chemical cross-linking usually gives rise to a heterogenous mixture of products, which can lead to irreproducible results in use of the complex.

Not only does Von Wussow fail to disclose the important structural features noted above, he provides no suggestion to modify his complex to achieve the claimed invention. Von Wussow indicates that the purpose of linking INF-α to an immunoglobulin was merely to increase the half-life of circulating INF-α. Von Wussow fails to recognize the advantages of combining a ligand of known binding specificity with the effector functions of an immunoglobulin (in contrast to attempting to select a natural immunoglobulin having the same binding characteristics as the ligand). Absent disclosure of this advantage of the claimed immunoligands, one of ordinary skill would lack motivation to attempt to produce them.

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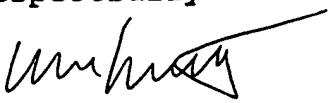
The nonobviousness of the claimed immunoligands is further substantiated by their unexpected properties. The combination of an IL-2 ligand with an immunoglobulin constant region into a single contiguous peptide molecule places conformational constraints on the respective components, which would have had an unpredictable effect on their respective functions (e.g., binding to the IL-2 receptor, complement fixation and ADCC activity). Surprisingly, it has been found that the claimed immunoligands exhibit functional properties of both components, namely capacity of IL-2 ligand to bind to its receptor and capacity of the immunoglobulin constant region to effect complement-dependent cell lysis. Still more surprisingly, the immunoglobulin constant region component also exhibits ADCC activity, which is not shown by the native murine immunoglobulin from which the constant region component was derived. These surprising results are entirely unpredictable from Von Wussow's work. In Von Wussow's complex, the ligand and immunoglobulin components are in a different physical linkage and therefore under different conformational constraints than the components of the claimed immunoglobulins. Moreover, as noted above, Von Wussow provides no indication that his complex has capacity for complement-dependent cytotoxicity or ADCC, much less that the claimed immunoligands would have these properties.

For all the above reasons, Applicants respectfully submit that the rejection of the claimed IL-2-immunoligands over Von Wussow should be withdrawn.

In light of the amendments to the claims, the application is in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at (415) 326-2400.

Respectfully submitted,



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